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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,546	12/08/2000	Celia Dominguez	A-648	4170

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EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/732,546

**Applicant(s)**

DOMINGUEZ ET AL.

**Examiner**

Deepak R Rao

**Art Unit**

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 June 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-19 are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-2, 4-19 are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This office action is in response to the amendment filed on June 26, 2002.

Claims 1-2 and 4-19 are pending in this application.

***The following rejections are withdrawn:***

The rejection under 35 U.S.C. 103(a) of the previous office action over U.S. Patent No. 5,721,366 is hereby withdrawn in view of the amendments. Applicant amended the claims to delete the term "amidino" from the definition of U. The reference compounds of formula (I) contain an amidino group [i.e.,  $-C(=NH)(NH_2)$ ] substituent on the phenyl which is attached to the pyrrolidin-2-one group. Further, the chain containing the terminal carboxylate group is attached to a different position of the pyrrolidin-2-one. The reference does not teach or fairly suggest any substituents analogous to U of the instant claims or different structural orientation for the pyrrolidin-2-one group. From the reference teachings, it would not have been obvious to a person of ordinary skill in the art first to replace the amidino with other substituent groups as recited in the instant claims and further to change the point of attachment of the pyrrolidin-2-one group.

***The following rejection is maintained:***

Claims 9-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of diseases such as rheumatoid arthritis, does not reasonably provide enablement for the treatment of all other diverse disorders embraced by the instant claims. The specification does not enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant's arguments citing MPEP § 2164.07 have been fully considered but they were not deemed to be persuasive. However, the claims were rejected because there was no enablement commensurate in scope with the claims, as provided in MPEP § 2164.08 which is particularly relevant to the instant situation. The instant claims are drawn to treatment of all types of diseases modulated by an integrin receptor and the specification does not provide sufficient enabling disclosure commensurate in scope with the claims. Regarding, integrins, a state of the art reference (<http://pharmrev.aspetjournals.org/cgi/content/full/50/2/197>) provides that 'integrins are a family of cell-surface glycoproteins that act as receptors for ECM proteins'; 'integrin-mediated cell adhesion regulates numerous biochemical activities'; and concludes that the 'integrins are a particularly complex family of cell adhesion receptors'. The reference clearly suggests that several issues regarding the pharmacokinetic aspects of these receptors remain to be resolved. The issue particularly with the instant claims is the correlation between the HUVEC cell proliferation assay and clinical efficacy for the treatment of the various diseases modulated by an integrin receptor and/or the treatment of inflammation, cancer, viral infections, etc.

*In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (Given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims, a rejection under 35 U.S.C. 112, first paragraph for lack of enablement was appropriate.).

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Applicant argues that the specification details how to make and/or use aspects of the invention with diverse examples of the compounds. Determining if any particular claimed compound would treat any particular cancer, inflammation, etc. would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials with a number of fundamentally different diseases, or testing them in an assay known to correlate to clinical efficacy of such treatment. There is a large degree of experimentation involved. There is no working example of treatment of any disease in man or animals.

According to the On-line Medical Dictionary at <http://cancerweb.ncl.ac.uk/omd/index.html>, angiogenesis is "The process of vascularisation of a tissue involving the development of new capillary blood vessels". As such it is a normal process occurring in healthy tissue, particular during development. This claim would read on inhibiting angiogenesis in mammals with below normal angiogenesis activity, inhibiting angiogenesis in mammals with normal angiogenesis activity, or in asymptomatic mammals with up-regulated angiogenesis activity.

The various publications cited in the IDS as well as those listed in the remarks have been fully considered and some were discussed in the previous office action, however, applicant has not provided any further explanation of the unpredictability or uncertainty issues raised in the state of the art.

***The following rejections are necessitated by the amendment:***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-2 and 4-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "provided that when U represents **amidino**, ...." in last two lines of the claim. There is insufficient antecedent basis for this limitation in the claim. The definition of U starting at line 6 has been amended to delete this term.

#### ***Allowable Subject Matter***

Claims 1-2, 4-8 and 19 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

#### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

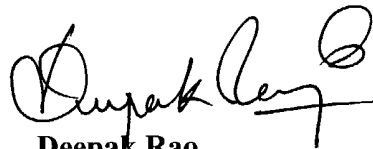
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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

A handwritten signature in black ink, appearing to read 'Deepak Rao', with a stylized flourish at the end.

**Deepak Rao**  
**Primary Examiner**  
**Art Unit 1624**

April 30, 2004